Remarks

Claims 19-33 and 36-38 are pending in the subject application. Applicants acknowledge that claims 21-24, 27-30 and 36 are withdrawn from consideration. By this Amendment, Applicants have amended claims 19, 21, 37 and 38 and added new claims 39 and 40. Support for the amendments to the claims can be found, for example, in the original claims and in the as-filed specification at pages 6-10. Entry and consideration of the amendments presented herein is respectfully requested. Accordingly, claims 19-20, 25-26, 31-33 and 37-40 are currently before the Examiner. Favorable consideration of the pending claims is respectfully requested.

Applicants gratefully acknowledge the Examiner's withdrawal of the rejections under 35 U.S.C. § 112, second paragraph, and objections to the specification.

Claims 19-20, 25-26, 31-33 and 37-38 are rejected under 35 U.S.C. § 112, second paragraph, as indefinite. By this Amendment, Applicants have amended the claims to clarify the terms. Accordingly, reconsideration and withdrawal of the rejection under 35 U.S.C. § 112, second paragraph, is respectfully requested.

Claims 19-20, 25-26, 31-33 and 37-38 are rejected under 35 U.S.C. § 103(a) as obvious over Handelsman *et al.* (U.S. Patent No. 7,008,767) in view of Hoch *et al.* (U.S. Patent No. 6,368,793). Applicants respectfully traverse and request reconsideration of the rejection.

The present invention is directed to a novel method for selecting or preparing cells comprising at least one metabolic pathway or metabolic pathway family enabling the transformation of at least one substrate {Ai} into a desired product {B} (specification at page 6, lines 6-11). Specifically, the present selection method comprises: transforming a population of host cells (Ai- ; B-) with a library of sequences of nucleic acid; and testing the growth capacity of host cells in parallel on a medium containing at least one substrate {Ai}, and at the same time, on a separate minimum medium containing the product (specification at page 27, lines 30-32).

Handelsman *et al.* provides a method for identifying genes and gene products from uncultivated microbial organisms by heterologous expression of genomic DNA isolated from uncultivated microorganisms in host cells (Handelsman specification at column 2, lines 9-12, 22-28; claim 1). Specifically, the Handelsman *et al.* method involves the steps of: transfecting host cells containing a vector including genomic DNA isolated from a source of uncultivated microorganisms;

and identifying gene products by detecting a compound produced by the transfected host cells relative to host cells lacking the genomic DNA (Handelsman *et al.* specification at column 2, lines 9-12, 43-50). The Office Action asserts at page 4 that Handelsman *et al.* disclose "a method for identifying non-proteinaceous compounds produced by a[n] uncultivated microorganisms, comprising i) generating a library of host microorganisms (populations of cells, as claimed in claim 19) . . ." (emphasis added). However, claim 19 of the present invention explicitly reads as "transforming [a] population of host cells with a library of sequences of nucleic acid" (emphasis added). It is clear that "a library of sequences of nucleic acid", as claimed in the present invention, is completely different from "a library of host microorganisms" in Handelsman *et al.*

Applicants further note that Handelsman *et al.* differs from the present invention in several additional aspects. First, Handelsman *et al.* simply relates to the detection of gene products by comparing gene products of transfected host cells to that of non-transfected host cells (Handelsman *et al.* specification at column 2, lines 43-50). However, there is neither explicit nor implicit teaching of any method in Handelsman *et al.*, which allows determining the transformation of a desired product from one or more substrate(s) as is claimed in the present invention. Indeed, the Office Action points to no teaching in Handelsman regarding the culturing of a transfected host cell on a first minimum medium containing at least one substrate and a second minimum medium containing a chosen product.

Secondly, the Office Action at page 11 asserts that the parallel testing is taught, or at least suggested, based on the premise that Handelsman *et al.* provide definition of a "biosynthetic pathway," which reads as "a set of anabolic or catabolic biochemical reactions for converting (transmitting) one chemical species into another." (Handelsman *et al.* specification at page 8, lines 40-43). Applicants respectfully point out that the mere definition of "biosynthetic pathway" does not teach any solution to the problem of how to determine the transformation of substrates into metabolic products, as is claimed in the present invention.

Furthermore, Handelsman *et al.* is completely silent on the detection method of parallel testing in the present invention, where host cells are selected on a medium containing at least one substrate as the only source of an element essential to growth, and at the same time, on a separate medium containing the product as the only source of an element essential to growth. In the present

invention, testing cells on a medium containing substrate {Ai} allows selection of cells capable of metabolizing substrate {Ai}; while simultaneous testing cells on a separate medium containing product {B} enables selection of cells capable of using {B} for growth. This confers a clear advantage. Specifically, the simultaneous testing of cells on a medium containing product {B} further ensures that substrate {Ai} is indeed converted to product {B}, not some other metabolic compound in the selected cells. This novel parallel testing step is not envisioned by Handelsman *et al.* In fact, the Office Action acknowledges at page 11 that "this seems to also go against the conventional wisdom in the art of determining the transformed product of the substrates (genes) to determine the transformed product of the substrate or cells that produce said product."

In contrast to the presently claimed invention, the detection method used by Handelsman *et al.* (Office Action at page 11 ("e.g., col. 25, lines 30-34")), involves the detection of the desired product by a phenotypical or optical modification of the cells. Indeed, the Office Action at page 6 acknowledges that Handelsman *et al.* do not disclose "that the only source of an element essential to growth is either the substrate or the product produced by the biosynthetic pathway." Therefore, Handelsman *et al.* simply relate to the detection of gene products. It fails completely to teach any solution to the problem for determining the transformation of a desired product from substrate(s) as is claimed in the present invention. Additionally, the novel parallel testing method in the present invention is never taught nor suggested in Handelsman *et al.* The secondary reference, Hoch *et al.* fails to cure the deficiencies noted above for Handelsman *et al.* Hoch *et al.* teach a method of first isolating microbial organisms capable of metabolizing a target compound "T", but not a source compound "S", to an essential factor (Hoch *et al.* at column 1, lines 54-57). Specifically, the Hoch *et al.* method comprises: "providing a cell containing one or more genes responsible for converting a target compound to provide a detectible signal, . . . wherein said detectible signal is not produced in the presence of said source compound; . . . and identifying cell that produces a said detectable signal in the presence of said source compound and the inducer of said promoter, but not in the presence of said source compound and absence of said inducer" (Hoch *et al.* at claim 1). This is opposite of what the present invention teaches and claims. The parallel testing method in claim 19 explicitly requires selection of cells based on cell growth which is a detectible signal, in the presence of the substrate and the product to obtain the desired phenotype (Ai+ ; B+).

As the Patent Office is aware, all the claim limitations must be taught or suggested by the prior art in order to establish a *prima facie* case of obviousness. *In re Royka*, 490 F.2d 981, 180 U.S.P.Q. 580 (C.C.P.A. 1974). Furthermore, "a patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 41 (2007). The Examiner is required to explicitly demonstrate that "there was an apparent reason to combine the known elements in the fashion claimed" by the applicant, "other than the hindsight gleaned from the invention itself." *Interconnect Planning Corp. v. Feil,* 774 F.2d 1132, 1143 (Fed. Cir. 1985), *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 41 (2007). Finally, it is improper to combine references where the references teach away from their combination. *In re Grasselli*, 713 F.2d 731, 743, 218 U.S.P.Q. 769, 779 (Fed. Cir. 1983). Thus, a *prima facie* case of obviousness may also be rebutted by showing that the art teaches away from the claimed invention. *In re Geisler*, 116 F.3d 1465, 1471, 43 USPQ2d 1362, 1366 (Fed. Cir. 1997). Thus, Applicants submit that a *prima facie* case of obviousness has not been established by the Patent Office as the combination of references fails to teach each and every limitation of the claimed invention and Hoch *et al.* explicitly teach away from the presently claimed invention. Accordingly, reconsideration and withdrawal of the rejection under 35 U.S.C. § 103(a) is respectfully requested.

It should be understood that the amendments presented herein have been made solely to expedite prosecution of the subject application to completion and should not be construed as an indication of Applicants' agreement with or acquiescence in the Examiner's position. Applicants expressly reserve the right to pursue the invention(s) disclosed in the subject application, including any subject matter canceled or not pursued during prosecution of the subject application, in a related application.

In view of the foregoing remarks and amendments to the claims, Applicants believe that the currently pending claims are in condition for allowance, and such action is respectfully requested.

The Commissioner is hereby authorized to charge any fees under 37 CFR §§1.16 or 1.17 as required by this paper to Deposit Account No. 19-0065.

Applicants invite the Examiner to call the undersigned if clarification is needed on any of this response, or if the Examiner believes a telephonic interview would expedite the prosecution of the subject application to completion.

Respectfully submitted,

Frank C. Eisenschenk, Ph.D.
Patent Attorney
Registration No. 45,332
Phone No.: 352-375-8100
Fax No.: 352-372-5800
Address: P.O. Box 142950
Gainesville, FL 32614-2950

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